## REMARKS/ARGUMENTS

Applicant would like to thank the Examiner for the careful consideration given the present application in the Office Action of April 18, 2008. The application has been carefully reviewed in light of the Office Action and amended as deemed necessary and appropriate to place the claims into condition for allowance or to place the application into better condition for appeal.

Specifically, by this Amendment claim 44 has been amended. No claims have been canceled and no new claims have been added to the application. Accordingly, claims 1, 2-9, 11-17, 23-26, 28-37, 39-42 and 44-46 are pending in the application, with claims 23-25 having previously been withdrawn from consideration. No new matter has been added to the application by this Amendment.

In the prior Office Action, the Examiner rejected claim 44 under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The Examiner noted that there was insufficient antecedent basis for the phrase "the mixture" in claim 44. By this amendment, the phrase has been amended to read as "a mixture." In view of the amendment to claim 44, reconsideration of the claim rejection under 35 U.S.C. §112, second paragraph is respectfully requested.

Also in the prior Office Action, the Examiner rejected claims 1, 3-9, 11-17, 26, 40-42, 44 and 45 under 35 U.S.C. §103(a) as being unpatentable over Milligan et al. (Anaesthesia 1998, 43, 563-564) in view of Bawa et al. (U.S. Pat. 6,261,547), Goldenheim et al. (U.S. Pat. 6,248,345), Arias-Alvarez (U.S. Pat. 4,657,764) and Strichartz (Regional Anesthesia and Pain Medicine 1998, 23(1), 3-6). For the reasons set forth below, applicant respectfully submits that the claims are clearly

patentable over Milligan et al., Bawa et al., Goldenheim et al., Arias-Alvarez and Strichartz. Withdrawal of the claim rejections is therefore respectfully requested.

Milligan et al. discloses a double-blind study in which doses of 0.25% and 0.5% bupivacaine were injected into the knee joint after arthroscopy. Milligan et al. report in the summary that "intra-articular bupivacaine had no significant (post operative) analgesic effect in either concentration". In the discussion section, Milligan et al. note that the plasma levels were all determined to be below toxic plasma bupivacaine concentrations in man. The authors stated that while this might support a case for the use of higher concentrations of bupivacaine, they did not propose to undertake such a study for two reasons: (1) the bupivacaine molecules would likely traverse the synovium rapidly and thus cause plasma concentrations to increase (implying, of course, that there would be an increased risk that systemically toxic concentrations could be achieved in the plasma); and (2) it would not likely be effective because the lack of any significant analgesic effect suggested that **the source of pain after arthroscopy was likely outside the capsule of the knee joint**.

The Examiner contends that in view of Milligan et al., one of ordinary skill in the art would have been motivated to inject bupivacaine into a post-operative joint space at higher concentrations because Milligan et al. teach that a concentration of 0.5% provided little analgesia and because Milligan et al. noted that in view of the plasma levels, a case could be made for the use of higher concentrations. But this contention runs contrary to the clear teaching of Milligan et al. Milligan et al. does not suggest that one should use higher concentrations of bupivacaine to achieve a long-term analgesic effect because **the source of pain after arthroscopy was**

**likely outside the capsule of the knee joint**. Thus, no person of ordinary skill in the art would be motivated by the teachings of Milligan et al. to inject bupivacaine at a higher concentration into the post-operative joint, and would not have had any expectation that doing so would produce any beneficial effect.

The Examiner contends that Strichartz cures the deficiencies in the teachings of Milligan et al. Strichartz is an editorial discussing a case report authored by Choi YK et al., which was published in Reg. Anesth. Pain Med. 1998, 23: 96-100. A copy of Choi et al. is attached hereto for the Examiner's convenience. In his Editorial, Strichartz notes that Choi et al. injected three (3) patients suffering from chronic painful conditions with a 5% lidocaine solution. The injection sites (which are reported in Choi et al.) were: a mandibular nerve (Case 1); occipital nerves (Case 2); and an intercostal nerve (Case 3). Strichartz notes that relatively long-lasting pain relief was obtained in each case, but also indicates that pain returned in each case. **None of the injection sites in Choi et al. were post-operative join spaces**.

The Examiner contends that one having ordinary skill in the art would have found it obvious to inject a 5% lidocaine solution into a post-operative joint space as a one time application in an amount sufficient to entail neurolysis (and would have increased the concentration to 6%) in view of Milligan et al. and Strichartz. Applicant respectfully disagrees. Milligan et al. suggests that the source of post operative joint pain is **likely outside the capsule of the knee joint**, and Strichartz questions whether a neurolytic explanation for the pain relief observed in the three reported cases is plausible. Strichartz notes that the mechanism of pain relief in the Choi et al. case reports is uncertain, and that nerve lysis is unlikely to be the mechanism. Strichartz characterizes Choi et al. as "futuristic, intriguing and exciting", and then

concludes that more trials are necessary in order to "convince us that neurolysis with a commonly used anesthetic is no humbug."

Thus, one having skill in the art would not have found applicant's claimed invention obvious based on the combined teachings of Milligan et al. and Strichartz. Milligan et al. fairly teaches that the source of post operative joint pain is **likely outside the capsule of the knee joint**. And Strichartz questions whether a neurolytic mechanism can explain the three cases reported by Choi et al. This clearly contradicts the Examiner's contention that the "concept of high concentrations of local anesthetics being neurolytic is known in the art and not anything new."

The determination regarding whether an invention as claimed is obvious in view of the prior art must be made in accordance with the standards set forth in the Supreme Court's opinion in *KSR International Co. v. Teleflex Inc.*, 550 U.S. ___ , 82 U.S.P.Q.2d 1385 (2007). In the *KSR* case, the Court made it clear that in order to reject a claim under 35 U.S.C. §103, there must be an explicit analysis explaining the apparent reason why a person of ordinary skill in the art would combine known elements described in the prior art in the way claimed. The person of ordinary skill in the art would have to see the benefit of making the combination. The person of ordinary skill in the art would have to recognize that it would improve similar devices or methods in the same way. The critical inquiry is whether the claimed improvement is more than the predictable use of prior-art elements according to their established functions. If it is, then the improvement is not obvious under 35 U.S.C. §103(a). In the present case, the analysis required by *KSR* requires a finding that applicant's invention, as claimed, is not obvious in view of Milligan et al. and Strichartz.

The additional references the Examiner attempts to combine with Milligan et al. (Bawa et al., Goldenheim et al. and Arias-Alvarez) do not overcome the deficiencies noted in the teachings set forth in Milligan et al. and Strichartz. None of these references suggest injecting concentrations of amide local anesthetics into post-operative joint spaces sufficient to entail neurolysis. Bawa et al. relates to an ophthalmic composition, which is an external optical application of an anesthetic drug to the eye. The mechanism employed in Bawa et al. is not neurolysis, but rather it is sustained release. It is wholly inapposite.

Goldenheim et al. discloses the use of local anesthetics in joints, but again does not disclose or suggest the use of neurotoxic concentrations of local anesthetics for any beneficial purpose. Goldenheim et al. discloses a sustained release composition. Again, the mechanism would be the same analgesia as commonly produced through the use of local anesthetics, and not neurolysis.

Arias-Alvarez only relates to the use of sodium bisulphate, which is addressed only in a dependent claim. Arias-Alvarez cannot be relied upon to cure the deficiencies in the teachings of Milligan et al. and Strichartz.

The Examiner also rejected claims 1, 3-8, 11, 13, 26, 28, 35 and 40-42 under 35 U.S.C. §103(a) as being unpatentable over Macek et al. (U.S. Pat. 3,368,937). Macek et al. discloses an injectable steroid solution comprising an anti-inflammatory steroid and a local anesthetic. Macek et al. teach that the steroid solution can be administered by intramuscular, intrasynovial, intra-articular and soft-tissue injection. Clearly, the concentration of local anesthetic in the steroid solutions according to Macek et al. do not make them predominantly toxic to nociceptive nerve fibers, and thus would not be of a sufficient concentration to entail neurolysis. If that were the

case, one can only imagine the problems that would follow subsequent to intramuscular administration of the composition, which is expressly suggested by Macek et al.

Like Milligan et al., Macek et al. clearly does not teach or suggest applicant's surprising method of treating post-operative joint pain. Macek et al. does not appreciate that amide local anesthetics, when injected into the post-operative joint space at appropriate concentrations, can entail neurolysis that provides a long-lasting (months to years) analgesic effect. This is not suggested by Macek et al. And one having ordinary skill in the art would not have been motivated to arrive at applicant's method, as claimed, in view of the teachings of Macek et al. Macek et al. teaches one how to combine a steroid with a local anesthetic in a concentration well-below where neurolysis would occur, such that the steroid solution is quick-acting and exhibits a long shelf-life.

Next, the Examiner rejected claims 1, 5, 28-37, 39 and 46 under 35 U.S.C. §103(a) as being unpatentable over Macek et al. in view of Goldenheim et al. and Strichartz, and with respect to claims 34 and 37 in view of Davis et al. (U.S. Pat. 3,917,830), and with respect to claim 39 in view of Herschler (U.S. Pat. 4,296,104), and with respect to claims 28-30 in view of Oakes et al. (U.S. Pat. 5,061,485) and with respect to claims 31 and 32 in view of Mueller (U.S. Pat. 5,002,761) and with respect to claim 36 in view of Chasin et al. (U.S. Pat. 5,942,241), and with respect to claim 33 in view of Klaveness (U.S. Pat. 5,242,683). Macek et al., Goldenheim et al. and Strichartz have been discussed above. None of the references fairly teach injecting an agent comprising an amide local anesthetic in a concentration sufficient to cause neurolysis into a post-operative joint space for the purpose of achieving an

analgesic effect lasting for many months to years. Milligan et al. teaches injecting local anesthetics into joint spaces, but only in concentrations that would produce the known and expected short-term analgesic effect. Strichartz discusses three cases reported by Choi et al. in which higher concentrations of lidocaine were injected into sites **other than post-operative joint spaces**. Macek et al. teaches one skilled in the art how to prepare a steroid/local anesthetic composition that is quick-acting and has a long shelf life. Goldenheim et al. teaches one skilled in the art how to prepare a sustained release anesthetic formulation. But none of the references cited fairly teach or suggest applicant's invention, which is a method of treating post-operative joint pain via the injection of an agent containing an amide local anesthetic in a concentration whereby neurolysis is effected. In view of the claim amendments and for the reasons set forth herein, applicant respectfully submits that the rejections under 35 U.S.C. §103(a) should be withdrawn.

Also in the prior Office Action, the Examiner provisionally rejected claims 1, 2, and 40-42 on the ground of non-statutory obviousness-type double patenting as being unpatentable over claims 50 and 51 of copending App. Ser. No. 11/722,779. The Examiner also provisionally rejected the same claims on the same grounds as being unpatentable over claims 39-42 of copending App. Ser. No. 11/722,857 and claims 94-96 of App. Ser. No. 11/722,484. Applicant reserves the right to submit a terminal disclaimer to obviate the double patenting rejections.

In light of the foregoing, it is respectfully submitted that the present application is in a condition for allowance and notice to that effect is hereby requested. If it is determined that the application is not in a condition for allowance, the Examiner is

invited to initiate a telephone interview with the undersigned attorney to expedite prosecution of the present application.

If there are any additional fees resulting from this communication, please charge same to our Deposit Account No. 18-0160, our Order No. LUS-15874.

Respectfully submitted,

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